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Adult miniature swine were exposed to various levels and durations of +G_z. After exposure, all swine were euthanized and necropsied. Gross, histologic, and electronmicroscopic observations were made on the heart tissue. Subendocardial hemorrhage (SEH) was commonly found in the left ventricle, rarely in the right ventricle, and its severity was directly related to: a) level and duration of G exposure, b) heart rate, and c) catecholamine activity. SEH was made more severe with i.v. atropine 4 mg, and prevented with i.v. propranolol 20 mg. Heart hemorrhage was usually limited to the immediate subendocardial

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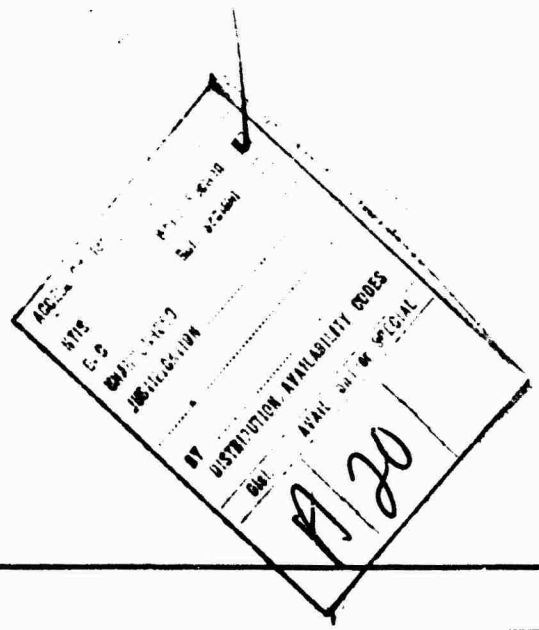
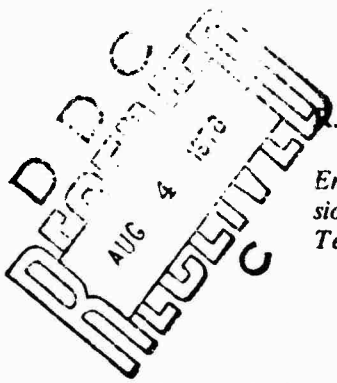


Cardiac Pathology Associated with High Sustained $+G_z$: I. Subendocardial Hemorrhage



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BURTON, R. R., and W. F. MACKENZIE. *Cardiac pathology associated with high sustained $+G_z$: I. Subendocardial hemorrhage.* Aviat. Space Environ. Med. 47(7):711-717, 1976.

Adult miniature swine were exposed to various levels and durations o $+G_z$. After exposure, all swine were euthanized and necropsied. Gross, histologic, and electronmicroscopic observations were made on the heart tissue. Subendocardial hemorrhage (SEH) was commonly found in the left ventricle, rarely in the right ventricle, and its severity was directly related to: a) level and duration of G exposure, b) heart rate, and c) catecholamine activity. SEH was made more severe with i.v. atropine 4 mg, and prevented with i.v. propranolol 20 mg. Heart hemorrhage was usually limited to the immediate subendocardial region and frequently surrounded Purkinje's fibers. In severe cases, however, hemorrhages penetrated several millimeters into the heart muscle and sometimes penetrated Purkinje's fibers. Restraint of unanesthetized swine in the centrifuge couch, low G-levels, and/or i.v. injections of atropine or epinephrine produced minimal SEH lesions.

EXPOSURE to high sustained $+G_z$ (HSG) "tolerable" to man has produced subendocardial hemorrhage (SEH) in adult miniature swine (6). Since diagnosing SEH in man is difficult, our laboratories were interested in identifying pathophysiologic situations in which SEH occurred in the swine. Comparing these situations with the occurrence of SEH in swine during $+G_z$ should suggest physiologic bases and limits necessary for occurrence of this lesion in man during HSG exposure.

Several similarities have been noted between SEH produced by $+G_z$ and by hemorrhagic shock (6). Studies of the heart lesions of hemorrhagic shock have suggested that several factors acting together may contribute to their formation; viz, a) tachycardia, b) reduced cardiac blood volume, and c) cardiac inotropism caused by high levels of circulating catecholamines (17). Since $+G_z$ apparently also produces these physiologic alterations, the following study was conducted examining these factors in SEH development in adult miniature swine.

As this study progressed, several pathologies involving heart muscle became apparent. These findings are reported by MacKenzie *et al.* (15).

MATERIALS AND METHODS

Adult female miniature swine were exposed to various acceleration levels, using the "animal end" of the centrifuge used for human experimentation at the Biodynamics Branch, USAF School of Aerospace Medicine (USAFSAM), Brooks AFB, Tx. Methods of exposing unanesthetized swine to acceleration, including anti-G suit application have been described in a previous report (4). Appropriate acceleration exposure levels, durations, and other experimental conditions, e.g., drug usage, will be specified in the Results section.

The pig was euthanized either immediately or 24 h after the final acceleration exposure, using several techniques described by MacKenzie *et al.* (15). They also describe the methods used in examining the heart tissue.

In the course of this study, it became apparent that some method of quantifying SEH severity would be useful. Consequently, a scoring system of 1 to 4 was devised—the number increasing with the severity of hemorrhage. A score of 1 indicated a slight barely visible hemorrhage involving only one area of no more than 1 cm^2. A score of 4, rarely used, indicated the most severe ventricular hemorrhage involving several areas of wall and papillary muscle and with each site usually several cm^2 in area. The left ventricular wall and papillary muscles were given individual hemorrhage scores which were summed to give the total heart SEH score; e.g., a maximum score of 8 was possible for one ventricle and 16 for both ventricles.

The research reported in this paper was conducted by personnel of the Environmental Sciences and Veterinary Sciences Divisions, USAF School of Aerospace Medicine.

The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources-National Research Council.

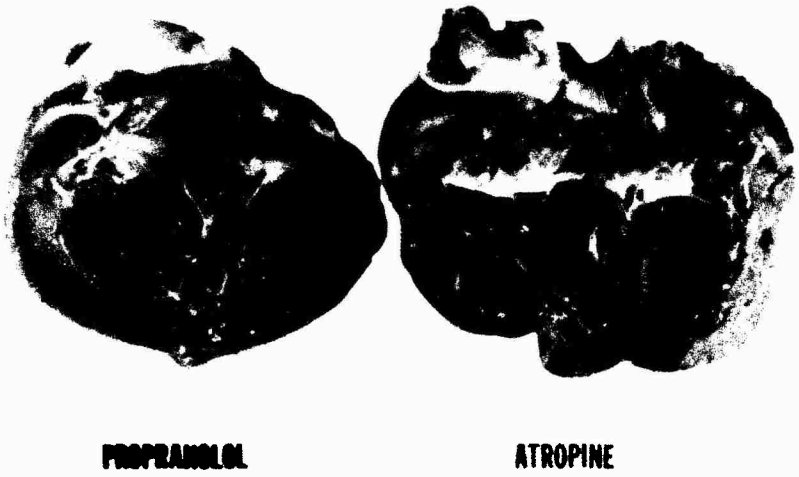

Fig. 1. Comparison of gross observations of two hearts of swine which had been exposed to 90 s of +9 G_z without an anti-G suit. Prior to centrifugation, one pig had received 4 mg atropine i.v. and the other, 20 mg propranolol i.v. The atropinized heart has a SEH score of 8; the other, a score of 0. Cuts on ventricular wall and papillary muscle are biopsy sites.

RESULTS

Pathology of SEH: SEH found during HSG exposure of swine appears to be similar to mural hemorrhages found in hemorrhagic shock as well as other stress conditions. SEH occurred on the prominence of the papillary muscles in the basal one-third of the left ventricular wall (Fig. 1). The depressions between chordae tendineae and between papillary muscles and the apical one-third of the ventricular wall were usually spared. Cardiac hemorrhage appeared as streaks and smudges rather than the punctate spots seen in other tissues. Apparently, this difference in the appearance of hemorrhage in cardiac muscle is due to the contractions of the heart moving the erythrocytes beneath the endocardium. In moderately severe lesions, the SEH was confined to the subendocardial connective tissue, however, in more severe cases, the hemorrhage extended several millimeters into the myocardium. SEH was rarely found in the right ventricle and then only in the most severe situations.

Histopathology of SEH revealed extravasated erythrocytes in the interstitium of the subendocardial tissues, frequently surrounding Purkinje's fibers (Fig. 2). The relatively diffuse hemorrhage and lack of well-defined clots suggested that capillaries or very small veins were the injured blood vessels. In severe cases, red blood cells were frequently seen in the adventitia of blood vessels and between muscle fibers. It appeared that erythrocytes actually dissected the connective tissue and sarcolemma of Purkinje's fibers. There was slight pathologic reaction to the hemorrhage; e.g., the presence of an occasional macrophage. In more severe cases, erythrocytes were found inside Purkinje's fibers (Fig. 3). Erythrocytes were also found in necrotic cardiac muscle fibers—degeneration and necrosis of working muscle fibers after HSG exposure are discussed in detail by MacKenzie *et al.* (15). Physical injury to blood vessels was not always evident during histologic examination of lesions of hemorrhage.

Additional evidence of damage to Purkinje's fibers was found in the electrocardiogram (ECG) of one pig

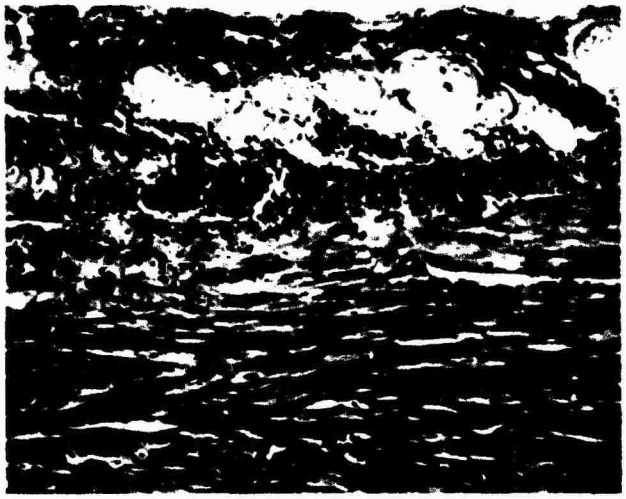

Fig. 2. SEH lesion showing erythrocytes in the subendocardium surrounding Purkinje's fibers. Masson stain X 167.

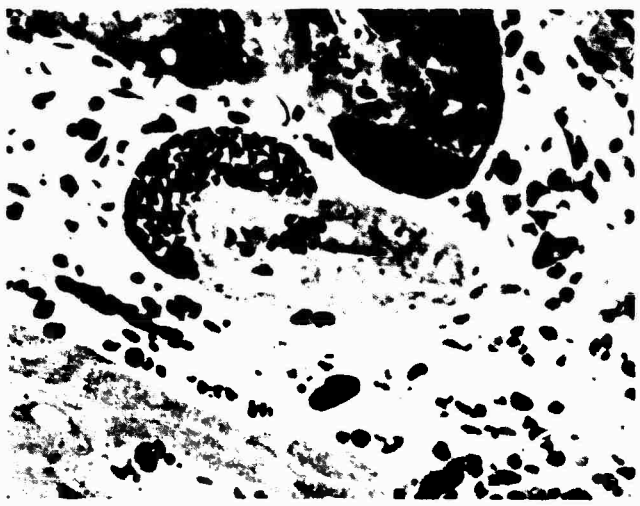

Fig. 3. Plastic-embedded 1-μ section of subendocardial Purkinje's fiber showing hemorrhage surrounding fibers and filling sarcolemmal tube. Arrow denotes erythrocytes within Pukinje's fiber.

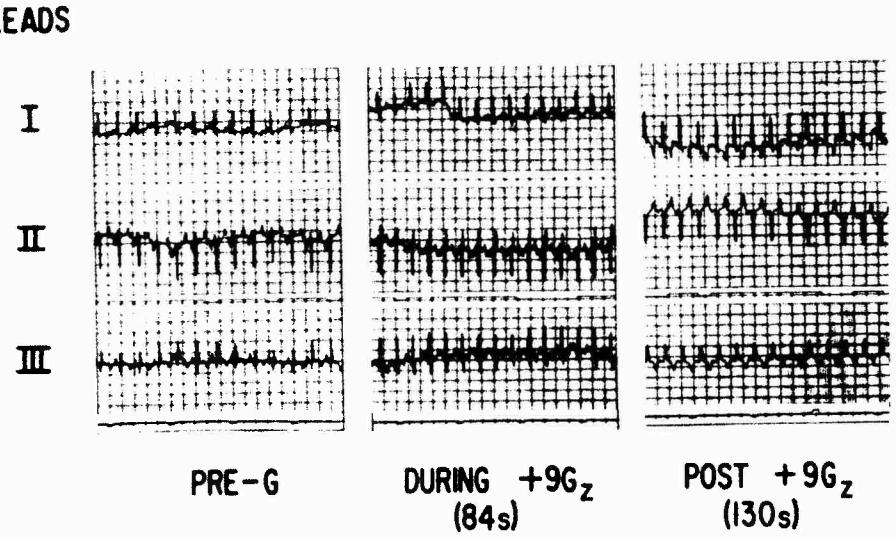

Fig. 4. Pre-G ECGs (leads I, II, and III) compared with ECGs from the same pig during (84 s) and after (130 s) exposure to +9 G_z for 90 s.

with severe SEH (pathology score of 10) after exposure to HSG. During exposure to +9 G_z for 90 s without an anti-G suit, the pig showed a widening of the QRS relative to the pre-G ECG. A widened QRS was still in evidence 130 s after the HSG exposure, when the pig was removed from the centrifuge (Fig. 4).

Electron microscopy of SEH eliminated degenerative changes in blood vessels as a possible etiology of the hemorrhage. The endothelial cells were healthy and the intercellular junctions were tight. Although we did not specifically search for injured blood vessels, one ruptured subendocardial capillary was found (Fig. 5). In the myocardium, extravasated erythrocytes surrounded capillaries and were squeezed in between individual myocytes. There was also considerable intercellular edema but little fibrin. Small blood vessels in this area were structurally normal but showed some distortion apparently due to the hypercontraction of surrounding muscle cells. A few scattered leucocytes were found with the extravasated red blood cells but were numerous only around necrotic muscle cells—discussed in the article by MacKenzie *et al.* (15). No obvious erythrophagocytosis was noted on light microscopy.

Incidence of SEH: We began our study by establishing a relationship between G-exposure (G level × duration (s) × 10^{-2}) and the incidence of SEH, using 29 adult female miniature swine, as shown in Fig. 6. Pigs with SEH scores over 4 had been exposed to +9 G_z for 15 to 90 s; those with SEH scores less than 4, to +7 G_z for 45 s or less. All 29 pigs appeared to remain conscious—as evidenced by the sound of conscious "grunting" by the pig—for the entire duration of G exposure.

The correlation coefficient of 0.76 (Fig. 6) between SEH and G exposure is statistically significant ($p < 0.01$); however, two pigs with high G exposure scores (6.8 and 8.1, which included 60 to 90 s of +9 G_z) did not develop SEH. For the pig to be useful as an animal model for studies concerned with SEH and HSG, the occurrence of SEH must be predictable; so at that time we felt that a greater understanding of SEH was necessary.

Fig. 5. Electromicrograph of subendothelial capillary (C). Neutrophil (N) is exiting through a break in the vessel wall. The break in the capillary did not occur at a cell junction. Note the healthy appearance of the endothelial cells, (M) cardiac muscle cell, (R) erythrocyte; x 4100.

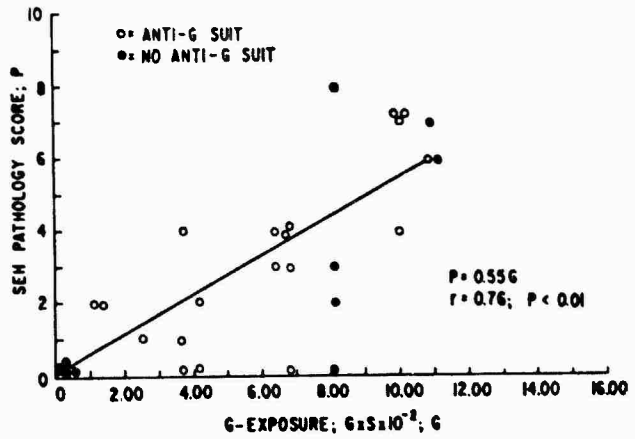

Fig. 6. Relationship (direct correlation) between G exposure (G × duration (s) × 10^{-2}) and SEH pathology score in 29 adult female miniature swine.

Heart Rate Relationship to SEH: Heart rate in the pig during HSG exposure is not predictable. During the first few seconds, a sinus tachycardia usually occurs; viz, a range of 200 to 250 heart beats/min (bpm). If high G exposure continues, however, the heart usually slows, either gradually or abruptly. An extreme bradycardia of 40 bpm has been observed during +9 G_z exposures.

A slow heart rate during HSG seems to have some correlation with the absence of SEH; e.g., the two pigs that had G exposure scores of 6.8 and 8.1 and did not exhibit SEH (Fig. 6) had maximum heart rates of 120 and 140 during the high G exposure. All the other pigs with this much G exposure had maximum heart rates of at least 200, and all had some SEH.

The physiologic basis for this usual slow heart rate during G was considered by giving 4 mg atropine i.v. in four pigs just prior to a 90-s G exposure of either +9 or +15 G_z. All these pigs had higher heart rates than usually found during HSG, and all had high SEH scores (Table I). Since atropine prevented some of the high G bradycardia, it appears that some, but not all, of this reduction in heart rate during G is extracardial, probably having a vagal origin. A pig exposed to 120 s of +15 G_z without an anti-G suit had a low heart rate, except for a brief transient increase to 200 bpm at 60 s, and this pig did not exhibit SEH.

Heart rate was increased in one pig during exposure to HSG by pacing the heart at 240 bpm, using an intravascular pacing electrode introduced into the right ventricle via the jugular vein. This pig had severe SEH (score of 6).

Heart rate was slowed in three pigs by injecting 20 mg (0.4 mg/kg body mass) of propranolol i.v. immediately prior to HSG exposure—after the pigs had been restrained on the centrifuge. These had slower heart rates during HSG exposure than either control pigs (HSG without drugs) or atropinized pigs. As shown in Table I, the propranolol pigs did not exhibit SEH (Fig. 1); however, as determined later, propranolol effects involved more than a reduction in heart rate.

In man, positioning the long axis of the body perpendicular to the G vector (G_x-type exposure) reduces the tachycardia accompanying HSG—offering some degree of G protection (3,5). A reduction in heart rate during HSG by changing body position relative to the G vector was attempted using two pigs. Both pigs were positioned 65° from the +G_z vector and exposed to 9 G for 90 s without anti-G suits. One pig exhibited a mean heart rate of 142 bpm for the entire 90-s G run, whereas the other pig had a mean heart rate of 202 bpm. The former pig had no SEH, and the latter pig had an SEH score of 6.

Using exposures of +7 G_z or less with 10 pigs, we considered the effects on the subendocardium of a high heart rate coupled with exposures of low-level +G_z or restraint only with the pig lying on its back (+1 G_x) in the couch. Low levels of +G_z (+3 G_z for 45 s) or drugs which increase heart rate—epinephrine or atropine—can produce minimum SEH. Short-duration couch restraint alone apparently does not produce SEH.

Sympathetic/Stress Responses to HSG: Cardiovascular injury resulting from high levels of circulating sympathetic catecholamines is well documented and has recently been reviewed by Haft (12). SEH is frequently included in cardiovascular injuries with this origin.

Consequently, plasma levels of epinephrine and norepinephrine were determined on venous blood taken from 10 pigs immediately prior to and after HSG exposure.* Another plasma sample was taken 24 h later. Venous sampling techniques—identical for all three samples—involved physically restraining the pig on its back and withdrawing blood from the supraorbital sinus, using a 1.5-in (3.8-cm) 21-ga needle attached to a 10-cm^3 plastic syringe. Two other pigs were similarly restrained and sampled but were not exposed to +G_z; they served as acceleration control animals. Restraint control values were determined using two pigs, each of which had an i.v. catheter implanted 2 weeks prior to blood sampling. This catheter exited out the back of the pig, allowing for venous blood samples—a total of two samples/pig/day for 5 d—to be taken without disturbing the pig. The catecholamine data are found in Table II.

Restraint appeared to immediately increase catecholamine levels above nonrestrained levels; e.g., in pre-G and 24-h post-G groups vs. the restraint control group, epinephrine increased approximately twofold whereas norepinephrine increased three- to fourfold. High, sustained G-exposures generally produced some additional increases in epinephrine but not norepinephrine; but in the +15 G_z group, increases in both catecholamines were evident. (Incidentally, +15 G_z is more acceleration than pigs can tolerate without losing consciousness.) Therefore, both physical restraint and HSG exposure apparently produce an increase in catecholamine levels.

Physiologic stress was quantified using circulating plasma levels of cortisol in some of these same pigs. Although acceleration and restraint controls were not available, levels of 9.09 $\mu g\%$ immediately before and after

TABLE I. RELATIONSHIP OF HEART RATE TO SEH USING VARIOUS METHODS TO ALTER HEART RATE DURING HSG EXPOSURES OF 90 TO 120 s.

G level and conditions	N†	Heart Rates (s of G exposures) 0s	30s	60s	90s	120s	SEH score (mean)
+15 G_z	1	50	160	200	160	130	0
+15 G_z*	1	220	200	160	120	N.E.	8
+ 9 G_z	6	215	145	133	136	N.E.	5.3
+ 9 G_z#	2	130	100	100	100	N.E.	0
+ 9 G_z*	3	240	187	190	157	N.E.	7.0
+ 9 G_z**	3	170	120	110	110	N.E.	0

†Number of animals per group; *4 mg atropine i.v. prior to G exposure;
**20 mg propranolol i.v. prior to G exposure; N.E. = no exposure;
#Naturally occurring slow heart rate during HSG exposure.

*Plasma catecholamines and cortisol determinations were made by the Institute of Environmental Stress, University of California at Santa Barbara, Santa Barbara, Ca.

TABLE II. CATECHOLAMINES AND CORTISOL PLASMA LEVELS ($\mu g\%$) IN SWINE EXPOSED TO HSG AND THEIR CONTROLS (MEANS ± S.E.).

G level and conditions	N†	Epinephrine Pre-G	Epinephrine 24 h post-G	Norepinephrine Pre-G	Norepinephrine 24 h post-G	Cortisol Pre-G	Cortisol N†	Cortisol 24 h post-G	Cortisol N†
All groups	12	1.54 ± 0.46	1.76 ± 0.26	1.48 ± 0.63	1.15 ± 0.12	9.09 ± 1.10	10	5.94 ± 0.65	7
Restraint* control	2	0.84 ± 0.03		0.40 ± 0.23		—		—	
Acceleration** control	2	0.99 ± 0.16		0.68 ± 0.22		—		—	
		Immediate post-G		Immediate post-G		Immediate post-G			
+9 G_z − 90 s Propranolol	2	2.14 ± 0.97		1.29 ± 0.67		11.6 ± 2.18			2
9 G − 90 s 65° tilt	2	2.10 ± 0.63		1.55 ± 0.60		10.5 ± 0.42			2
+9 G_z (45 s to 90 s)	4	2.00 ± 0.75		1.31 ± 0.40		10.8 ± 0.14			2
+15 G_z (90 s)	2	3.65 ± 0.38		4.91 ± 1.37		—		—	
All 9 G	8	2.05 ± 0.41		1.37 ± 0.25		11.0 ± 0.61			6

† Number of animals per group.
* Two pigs were not restrained, bled two times/d for 5 d.
** Bleeding occurred at time intervals similar to groups exposed to HSG

TABLE III. THE EFFECT OF TACHYCARDIA, LOW LEVELS OF G EXPOSURE, AND DRUGS ON THE INCIDENCE OF SEH.

G*	Duration**	H.R.†	Drug	SEH (Score)
+7 G_z	15 s	220	none	1
+5 G_z	45 s	220	none	1
+5 G_z	15 s	210	none	2
+3 G_z	45 s	220	none	2
+1 G_x	—	100	none	0
+0.3G_z	45 s	100	none	0
+1 G_x	—	230	epinephrine i.v.††	1
+1 G_x	90 s	200	none	0
+1 G_x	90 s	210	none	0
+1 G_x	—	—	4 mg atropine i.v.	2

*Maximum G exposure; **Duration of maximum G-exposure; †Maximum heart rate (bpm); ††Epinephrine (1 - 1,000) injected until a maximum heart rate was obtained.

HSG exposure are high if compared to the 24-h post-G mean level of 5.94 $\mu g\%$.

Considering these data, restraint coupled with HSG exposure apparently increases the circulating catecholamines and cortisol, which represents a sympathetic/stress response.

We attempted to prevent direct catecholamine effect (inotropism) on the heart by injecting 20 mg propranolol i.v. just prior to HSG exposure. As noted previously in Table I, SEH was prevented; however, it was noted that propranolol prevented tachycardia, and this effect alone might have prevented the SEH. This heart rate effect was resolved by pacing (intracardial pacing electrode) two propranolol pigs at 240 bpm during exposure to HSG. Although their heart rates were maintained at 240 bpm for 90 s at +9 G_z, their SEH scores were greatly reduced (one pig did not show SEH, and the other pig had a low SEH score of only 1); i.e., apparently even though a tachycardia existed in conjunction with the cardiac stress of HSG, propranolol essentially prevented the occurrence of SEH.

Repeated Exposure to HSG: The effect of repeated occurrences of SEH was considered by exposing two pigs to 45 s each of + 5 G_z, + 7 G_z, and + 9 G_z, with 2-min rests between each G exposure. Each pig wore an anti-G suit and these exposures were repeated twice each week for 7 weeks. This type of G exposure was chosen because it is within the tolerance limits of both man and pig.

Gross and histopathology determinations were made on both pigs immediately after their last G exposure. No SEH was observed grossly or microscopically; however, staining with Perls' Prussian blue revealed slight hemosiderin deposits—evidence of prior occurrences of SEH. An increase in fibrous tissue in these hearts was not obvious. Some protective (adaptive?) mechanism had apparently prevented recent episodes of SEH in these pigs. Whether this protective mechanism was physiologic (functional) or anatomic (tissue) must be speculative at this time. In one pig, however, extreme reduction in heart rate was always seen at +9 G_z after the first HSG episode: the first exposure to +9 G_z found a heart rate of 130 bpm and regular at the end of the G exposure of 45 s, whereas the third +9 G_z exposure produced a heart rate of 40 bpm and irregular at the end of the run. This bradycardia may have "protected" the heart from subsequent SEHs. The other pig showed similar changes in heart rate, but on a less-regular basis.

DISCUSSION

HSG exposure is directly correlated to the occurrence of SEH in adult miniature swine (Fig. 6). SEH is generally limited to the area immediately beneath the endocardium, rarely involves cardiac muscle, and appears to

involve Purkinje's fibers. Involvement of Purkinje's fibers on occasion appears to slow the conduction of the electrical impulse over the ventricle.

Previous studies using other experimental animals have shown SEH of the left ventricle to be associated with high G exposure. Greenfield (11) reported SEH in cats following several 30-s exposures at 15-20 G. These animals were immersed in water during G exposures. Britton *et al.* (2) found SEH, especially involving the chordae tendineae of the left ventricle in monkeys, dogs, cats, and rats, subjected to high G forces. Gauer *et al.* (9) and Henry (13) demonstrated SEH in goats and dogs after negative G exposures. Our findings of SEH resulting from G exposure are not unique.

As determined in this study using adult miniature swine, SEH development during exposure to HSG appears to require, beside the general stress of HSG, a tachycardia (heart rates above 200 bpm) and catecholamine participation producing a positive inotropic effect on the heart. Preventing *either* the high heart rate or catecholamine effect on the heart (β blockage) will prevent the occurrence of SEH during exposure to HSG.

Although we know the physiologic factors necessary to produce SEH, little is known regarding the mechanism in the development of SEH. Henry (13), using goats exposed to $-G_z$, presented convincing evidence that SEH was not a result of increased arterial pressure, increased coronary sinus pressure, or tissue hypoxia. He concluded that, since the SEH appeared on prominences that fit into hollows on the opposing ventricular wall, the hemorrhage was the result of muscle wall squeezing rather than rubbing or shearing. On the other hand, Chiu *et al.* (8) found that in SEH experimentally caused by cardiopulmonary bypass, the ventricular endothelium was uninjured. Yet, when the ventricular endothelium rubbed on a fluid-filled Foley catheter, the endothelium became injured but without SEH. Consequently, they concluded that SEH lesions were due to uneven distribution of blood pressure in the myocardium as mediated through local ischemic and vasoactive regulatory factors. The work of Chiu *et al.* tends to exclude direct trauma as the causative agent of SEH, but it does not explain the distribution of hemorrhages, which is quite consistent, nor does it exclude the possibility that the balloon may have prevented SEH by separating the ventricular walls.

Our pathology studies showed no lesions in either the endothelial cells or the endocardium. The ruptured capillary shown in Fig. 5 suggests no cellular injury or degenerative change in the ruptured endothelial cells. We believe, therefore, that neither toxic, hypoxic, nor ischemic injury is the primary causative agent involved in producing SEH.

Regarding human experimentation at HSG, our group is particularly interested in the apparent necessity for tachycardia to be present before SEH can occur; i.e., both exposure to HSG and high catecholamine levels are not enough to produce SEH. Heart rate is always monitored (real time) during experimental exposures of humans to HSG, and the centrifuge is stopped if the heart rate is greater than 200 bpm. Our animal experiments suggest that a heart rate near 200 bpm, coupled with exposures of HSG, is the physiologic limit (minimum) required to produce SEH (Table I).

The use of a β blocking agent to prevent the possible occurrence of SEH in man is also a possibility. Recent experiments by Bjurstedt *et al.* (1) have demonstrated that propranolol used immediately prior to $+G_z$ exposure (i.v. 0.25 mg/kg body mass) appears to be safe and does not significantly affect tolerance to $+G_z$. They concluded that sympathetic chronotropism is not necessary for adequate circulatory adaptation to increased gravitational stress.

The pig appears to be an excellent "human analog" with which to study the relationship between HSG and SEH for two primary reasons: a) the adult miniature swine has acceleration tolerances similar to man's (4), and b) HSG readily produces SEH. Chang and Hackel (7) made similar observations in pigs regarding the production of SEH by hemorrhagic shock. They found pigs, cats, dogs, and man to develop similar heart lesions as a result of hemorrhagic shock. The use of the pig as a model with which to study heart pathology associated with HSG exposure has been criticized because of the ease with which SEH can be produced. On the other hand, using an animal naturally resistant to heart pathology to study heart pathology of HSG, would be incongruent and could only instill false confidence regarding the possible pathologic effects of HSG on man.

G levels above $+7$ G_z are required to produce moderate to severe SEH (pathology scores greater than 2), although minimal lesions can be produced at lower G levels with high heart rates and high catecholamine levels. SEH appears, therefore, as a lesion of HSG exposure, not a lesion of restraint or low G exposures.

We found no great functional significance in SEH as a one-time occurence, although in one case it slowed the electrical conductive properties of the heart and, as reported by Burton and MacKenzie (6), SEH appears to be resolved without incidence within 2 weeks. It is not clear, however, what pathologies would develop in the heart after several episodes of SEH: fibrous tissue buildup, especially in the papillary muscle, could produce some valvular insufficiency; also, some lesion could develop at the site of the insertion of the chordae tendineae which might cause it to rupture. Although we repeatedly exposed two pigs to HSG, they did not repeatedly suffer from SEH—apparently some adaptive mechanism prevented its recurrence.

SEH can occur in man. Shul'tsev and Teodori (19) reported SEH in several persons dying acutely following physical overexertion, and Martin *et al.* (16) found SEH in the left ventricle of a 20-year-old soldier who had died from battle wounds. Does man suffer from SEH during exposure to HSG? While experiments reported herein will not answer this question, this study does suggest that HSG is *potentially* a pathologic environment. Exposure to HSG initiates in animals—and probably in man as well—the pathophysiologic conditions necessary to produce SEH; viz, physiologic stress of $+G_z$ (e.g., a reduction in heart blood volume), tachycardia, and high levels of circulating catecholamines (14,18). Conse-

quently, these studies are relevant to human experimentation at HSG, if only to make investigators aware of the possible hazards of this environment. Human subjects therefore, must be closely monitored before, during, and after exposures to HSG. Several methods to detect the possible occurrence of heart pathology in man are presently used routinely at USAFSAM and will be reported in subsequent communications (10).

REFERENCES

1. Bjurstedt, H., G. Rosenhamer, and G. Tydin. 1974. Acceleration stress and effects of propranolol on cardiovascular responses. *Acta Physiol. Scan.* 90:491-500.
2. Britton, S. W., E. L. Corey, and G. A. Stewart. 1946. Effects of high acceleratory forces and their alleviation. *Am. J. Physiol.* 146:33-51.
3. Burns, J. W. 1975. Re-evaluation of a tilt-back seat as a means of increasing acceleration tolerance. *Aviat. Space Environ. Med.* 46:55-63.
4. Burton, R. R. 1973. Positive (+G_z) acceleration tolerances of the miniature swine: Application as a human analog. *Aerospace Med.* 44:294-298.
5. Burton, R. R., and R. W. Krutz, Jr. 1975. G-tolerance and protection associated with anti-G suit concepts. *Aviat. Space Environ. Med.* 46:119-124.
6. Burton, R. R., and W. F. MacKenzie. 1975. Heart pathology associated with exposure to high sustained +G_z: Joint Committee Aviation Pathology. *Aviat. Space. Environ. Med.* 46:1251-1254.
7. Chang, J., and D. B. Hackel. 1973. Comparative study of myocardial lesions in hemorrhagic shock. *Lab. Invest.* 28:641-647.
8. Chiu, J., W. A. Mersereau, and H. J. Scott. 1972. Subendocardial hemorrhagic necrosis. *J. Thor. and Cardiovas. Surg.* 64:66-75.
9. Gauer, O., J. P. Henry, E. E. Martin, and P. J. Maher. 1949. Arterial oxygen saturation and intracardiac pressures during acceleration in relation to cardiac damage. *Fed. Proc.* 8:54.
10. Gillingham, K. K., and P. P. Crump. 1976. Cardiac pathology associated with high sustained +G_z: III. Clinical measurements. *Aviat. Space Environ. Med.* 47:726-733.
11. Greenfield, A. D. M. 1945. Effect of acceleration on cats, with and without water immersion. *J. Physiol.* 104:5P-6P.
12. Haft, J. I. 1974. Cardiovascular injury induced by sympathetic catecholamines. *Prog. Cardiovas. Dis.* 17:73-86.
13. Henry, J. P. 1950. Studies of the physiology of negative acceleration. An approach to the problem of protection. USAF/AMC Tech. Rept. 5953.
14. Lindberg, E. F., W. F. Sutterer, H. W. Marshall, R. N. Headley, and E. H. Wood. 1960. Measurement of cardiac output during headward acceleration using dye-dilution technique. *Aerospace Med.* 31:817-834.
15. MacKenzie, W. F., R. R. Burton, and W. I. Butcher. 1976. Cardiac pathology associated with high sustained +G_z: II. Stress cardiomyopathy. *Aviat. Space Environ. Med.* 47: 718-725.
16. Martin, A. M., Jr., W. B. Green, R. L. Simmons, and H. B. Soloway. 1969. Human myocardial acute lesions. *Arch. Path.* 87:339-342.
17. Martin, A. M., D. B. Hackel, M. L. Entman, M. P. Capp, and M. S. Spach. 1969. Mechanisms in the development of myocardial lesions in hemorrhagic shock. *Ann. N Y. Acad. Sci.* 156:79-90.
18. Offerhaus, L., and J. C. Dejongh. 1967. Homeostatic regulation of the circulation during prolonged gravitational stress (+G_z). *Aerospace Med.* 38:468-474.
19. Shul'tsev, G. P., and M. I. Teodori. 1963. On myocardial hemorrhages and necrosis in physical overstrain. *Ark. Patol.* 25:33-38.

Transient psychosis could signal epilepsy

Unexplained transient psychotic episodes apparently are sometimes caused by epilepsy. Because observable seizures do not accompany the condition, electroencephalography must be done during a psychotic episode to establish the diagnosis. Long-term anticonvulsant therapy alleviates the disorder.

Ictal psychosis should be suspected when one or more of the following features are present: (1) abrupt onset of psychosis in a person who was previously psychologically healthy, (2) unexplained delirium, (3) a history of similar episodes with abrupt spontaneous exacerbations and remissions, and (4) a history of falling of fainting spells.

The EEG will show a more or less continuous spike-and-slow-wave discharge diffusely over both hemispheres during the occurrence of a psychotic episode.

Transient psychoses occurred in two patients and the histories of eight other patients were reviewed. All 10 patients, whose ages ranged from 10 to 75 years, had been diagnosed initially as having various psychiatric disorders ranging from delirium to acute catatonic schizophrenia. Epilepsy had not been diagnosed previously in three patients and was considered uncertain before the onset of the psychotic episode in one other patient.

CHARLES E. WELLS, MD, Vanderbilt University, Nashville, TN. Transient ictal psychosis. *Arch Gen Psychiatry* 32:1201-1203, 1975. For reprint: Dr Charles E. Wells, Dept of Psychiatry, Vanderbilt University, Nashville, Tn 37232.

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Cardiac Pathology Associated with High Sustained $+G_z$: II. Stress Cardiomyopathy

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The myocardial pathology of 14 pigs exposed to HSG_z stress of 9 and 15, or 3, 7, and 9 G_z was studied; six control pigs were used as comparisons. Four pigs received propranolol prior to centrifugation and four pigs received atropine. Hearts were studied by light and electron microscopy. Myocardium from stressed pigs showed myofibrillar degeneration, pooling of mitochondria, and cell death. Lesions occurred in random cells of the subendocardium and papillary muscles. Purkinje fibers were also involved. Pretreatment with atropine increased the number of dead cells found and propranolol increased the number of cells showing myofibrillar degeneration. It is postulated that this is a pluricausal cardiomyopathy similar to several experimental conditions. Significance to aerospace medicine is briefly discussed.

THE FIRST PAPER in this series (9) described the subendocardial hemorrhage found in pigs exposed to high sustained $+G_z$ (HSG_z); this second paper will describe the necrosis of myocytes that we have designated as stress cardiomyopathy. We have separated these entities into two papers because we believe they are distinct lesions with a different etiology, although they are often found together. Cardiomyopathy is the designation of a type of primary myocardial degeneration that is unassociated with vascular disease, hypertension, cor pulmonale, rheumatic or congenital heart disease or inflammation (6). The lesions in the pigs are histologically similar to or indistinguishable from many experimental cardiomyopathies produced by a variety of causes (7) often pluricausal (27,28,38,39). The pluricausal cardiomyopathies have only recently been recognized and their importance in heart disease is becoming increasingly appreciated (6,7,27,39). They are difficult to distinguish clinically and are usually diagnosed at necropsy (18). The early lesions are subtle and difficult to be seen in standard paraffin preparations, but are easily seen on 1-μ, plastic-embedded sections, electron microscopy is needed to completely define them.

Recognizing that the readers are not primarily morphologists, morphologic description is purposely held to a minimum and the emphasis in this paper is placed on discussing the findings.

MATERIALS AND METHODS

The methods of exposing the 20 pigs used in this study were detailed in the previous article (9), as was the use of atropine and propranolol. The severity of stresses given and the use of the drugs are shown in Table I. Control animals included: two pigs receiving 1 G_z to determine the effect of restraint and stress of the centrifuge, one pig receiving only the stress of restraint at necropsy, one pig tranquilized prior to necropsy, one pig receiving atropine, and one pig receiving propranolol.

New methods of fixation and tissue preparation had to be developed and are being published elsewhere, but a short description follows. The pigs were anesthetized with I.V. pentobarbitol. A tracheotomy was performed and the lungs oxygenated by hand. A large incision pro-

TABLE I. SUMMARY OF RESULTS OF HISTOLOGY STUDY OF HEARTS FROM 14 PIGS SUSTAINING $+HSG_z$ STRESS.

STRESS	Number of Pigs	Myofibrillar Degeneration	Necrosis of Myocytes
Control	4	0	0
1 G control	2	0	0
9 G_z 0.25 mg/kg propranolol	1	1	0
9 G_z 0.5 mg/kg propranolol	3	2, 3, 3	(a)
9 G_z 4 mg atropine	2	2, 2	2, 3
9 G_z then 9 G_z 4 mg atropine	1	2	3
15 G_z then 15 G_z 4 mg atropine	1	1	1
15 G_z	1	1	2
9 G_z	2	1, 2	2, 2
9 G 65°	2	1, 1	2, 0
3 G, 7 G, 9 G	1	2	3

(a) Single cell found necrotic in one pig.

The research reported in this paper was conducted by personnel of the Veterinary Sciences Division and Environmental Sciences Division, USAF School of Aerospace Medicine.

The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources—National Research Council.